The Influence of Marijuana Use on Neurocognitive Functioning in Adolescents

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Abstract: Marijuana use is common in adolescence, yet neural consequences have not been well delineated. This review seeks to ascertain whether heavy marijuana use in adolescence is associated with persistent neurocognitive abnormalities, and whether adolescents are more vulnerable to the impact of chronic marijuana use than adults.

Among heavy marijuana using adults, neurocognitive deficits are apparent for several days following use, but may disappear after one month of abstinence. Studies of adolescent heavy users have identified impairments in learning and working memory up to six weeks after cessation, suggesting persisting effects, yet raise the possibility that abnormalities may remit with a longer duration of abstinence.

Given ongoing neuromaturation during youth, adolescents may be more vulnerable to potential consequences of marijuana use than adults. This is supported by rodent models, which show greater memory impairments in animals exposed to cannabinoids as adolescents relative to those exposed as adults. Further, adult humans who initiated use in early adolescence show greater dysfunction than those who began use later. Together, these results suggest that adolescents are more vulnerable than adults to neurocognitive abnormalities associated with chronic heavy marijuana use; however, the impact of preexisting risk factors is unknown.

Adolescents demonstrate persisting deficits related to heavy marijuana use for at least six weeks following discontinuation, particularly in the domains of learning, memory, and working memory. Further, adolescents appear more adversely affected by heavy use than adults. Longitudinal studies will help ascertain whether preexisting differences contribute to these abnormalities.

Keywords: Adolescence, marijuana, cannabis, cognition, brain, development.

Marijuana is the most commonly used preparation of the psychoactive drug, Δ-9-tetrahydrocannabinol (THC), and is consistently the most widely used illicit drug among teenagers, and most users first experiment in adolescence [1]. While 17% of 8th graders have tried marijuana, by 12th grade almost half of teens have used [1, 2]. After initial experimentation, many youths develop a regular pattern of use, with 20% of 12th graders reporting use in the past month, and 5% of 12th graders reporting daily use [2]. Adolescence is also a period of continued neuromaturation, yet the potential neural consequences of marijuana use during these developments have not been well established, and may have implications for academic, occupational, and social achievements. This review will address two main questions:

1. Is adolescent marijuana use associated with persistent effects on neurocognitive functioning?
2. Are adolescents more vulnerable to the neural influence of marijuana use than adults?

To understand the influence of marijuana use on neurocognition, this review will examine evidence from neuropsychological studies as well as in-vivo measurements of brain functioning. To address the two main questions, some methodological issues must first be discussed. The question of the neural impact of adolescent marijuana use will then be considered, first by reviewing the adult literature, then by focusing on studies involving adolescent participants. Next, the question of adolescent vulnerability will be investigated by providing a brief overview of brain development in adolescence, then by examining rodent studies of cannabinoid administration among adolescents and adults, and finally evaluating human research on the age of initiating marijuana use among adults.

METHODOLOGICAL CONSIDERATIONS

Several methodological issues need to be discussed when attempting to determine the neurocognitive influence of chronic marijuana use among adolescents. First, heavy users of marijuana are more likely to use alcohol, nicotine, and other illicit substances. A recent study revealed that among adults with a lifetime marijuana use disorder (DSM-IV criteria for abuse or dependence), 82% also met criteria for an alcohol use disorder, and 48% met criteria for nicotine dependence [3]. Thus, among typical marijuana users, it is difficult to disentangle the neural effects of marijuana from those associated with other substances. However, studying users of soley marijuana may limit sample sizes, and results may not generalize to the typical population of heavy marijuana users. Heavy marijuana users are also more likely to

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have other comorbid psychiatric disorders [3], again making it difficult to disentangle the unique effects attributable to cannabis exposure distinct from attentional, mood, anxiety, or psychotic symptoms and related cognitive features.

Participant recruitment strategies must also be considered when reviewing studies of adolescent substance users. Individuals with cannabis use disorders often do not seek treatment [3]. The characteristics of adolescents in drug treatment may vary from adolescent marijuana users who are not in treatment, and cannot be equated with typical community adolescents. In particular, individuals in treatment manifest more severe substance use disorders, and poorer social, cognitive, and behavioral functioning [4]. Although adolescent marijuana users recruited through the community may better represent the population, these youths may be higher functioning than those in treatment, minimizing the ability to detect cannabis-related abnormalities.

Attempts must be made to match marijuana and control groups on a wide range of factors; however, it is virtually impossible to control for every domain that may contribute to cognitive functioning. Cross-sectional studies suffer from the inability to assess premorbid functioning, making it unclear whether marijuana users and non-users differed before the onset of marijuana involvement. Importantly, characteristics such as personality, social interactions, cognitive abilities, developmental stage, and emotional responses may contribute to the initiation of substance use, and may directly affect neurocognitive functioning. Thus, the developmental context in which adolescents use marijuana may influence neurocognitive outcome. Teens who initiate heavy marijuana use may differ from those who engage in experimentation or abstinence in terms of developmental stage or social environment, which may ultimately affect neurocognitive outcomes. While addressing the impact of these personal factors is beyond the scope of this review, their influence must be acknowledged when evaluating the research on adolescent marijuana use.

1. IS ADOLESCENT MARIJUANA USE ASSOCIATED WITH PERSISTENT EFFECTS ON BRAIN FUNCTIONING?

The goal of this paper is to review evidence of the influence of marijuana use on brain functioning in adolescents, yet few studies have been done in this area. Thus, a brief discussion of the adult literature will provide background for understanding the potential influence of marijuana use among adolescents.

Marijuana in Adults

A growing body of research has attempted to identify the neurocognitive effects of chronic marijuana use in adults, and the findings have been somewhat inconsistent. Adults who use marijuana chronically have demonstrated poorer performance on tests of learning and memory, attention, visuospatial skills, processing speed, and executive functions [5-11]. However, some investigations have found no performance decrements among heavy cannabis users [12-15]. A meta-analysis examined 11 studies that met strict inclusion criteria, and ascribed impaired learning and memory to chronic marijuana consumption, but determined that other cognitive domains remain unaffected [16].

Among heavy users, cannabinoid metabolites can remain detectable in the urine for an average of 27 days [17], and may continue to affect neural functioning. Pope and colleagues thus argue that deficits in attention, short-term memory, and psychomotor tasks following a short period of abstinence represent brief residual effects of cannabinoids, but that no persistent, long-term effects of chronic use exist in adults [12, 13, 18]. Marijuana users and controls aged 30 – 55 were tested 4 times over a 28-day period of supervised abstinence [12]. Compared to former users and non-using controls, current heavy users showed poorer verbal learning and memory performance after 0, 1, and 7 days of the abstinence. By day 28, however, heavy marijuana users were indistinguishable from former users and non-users, suggesting a lack of persisting neurocognitive effects of cannabis use in adults. In contrast, Bolla and colleagues [10] demonstrated that heavy cannabis users who underwent 28-day monitored abstinence periods continued to show cognitive deficits compared to published test norms. Greater quantity of marijuana use was associated with poorer performance on tests of visual learning and memory, executive functioning, and psychomotor speed, and greater duration of use was associated with compromised visuospatial reproduction.

Brain changes associated with marijuana use have been described with in-vivo measures of neural functioning. Electrophysiological evidence suggests alpha hyperfrontality associated with acute and long-term marijuana use, a pattern that may be unique to this substance [19]. Others have observed abnormal event-related potentials and poorer performance among marijuana users during selective attention, suggesting slowed information processing and difficulty focusing attention on relevant stimuli [20, 21]. Reduced resting cerebellar glucose metabolism [22] and frontal and cerebellar blood flow [23-25] have also been described among adult marijuana users. During verbal learning and memory, marijuana users showed poor recall performance associated with reduced prefrontal and cerebellar blood flow and abnormal hippocampal lateralization [26].

Recent functional magnetic resonance imaging (fMRI) investigations have begun to ascertain neural functioning among marijuana users during a variety of cognitive paradigms. Within 6 – 36 hours following use, marijuana users showed increased and widespread spatial working memory activation, both in anterior cingulate and prefrontal regions normally associated with spatial working memory, as well as in additionally recruited brain areas that were not activated among controls [27]. After one week of abstinence, marijuana users had similar fMRI response patterns as controls during verbal working memory, yet failed to show practice-related decreases in parietal activation [28]. During inhibitory processing, heavy marijuana users evidenced reduced anterior cingulate and greater mid-cingulate response, as well as more widespread bilateral dorsolateral prefrontal activation [29]. Moreover, both abstinent users and active users show brain response abnormalities relative to controls during visual attention [30], suggesting longer-lasting changes in patterns of neural activity. Together, these fMRI studies indicate altered brain response patterns among marijuana users despite similar task performance, suggesting increased neural effort and use of alternate strategies among marijuana users. Yet it remains unclear whether adolescents may be differentially impacted.

In summary, the impact of heavy marijuana use on neurocognition in adults generally indicates deficits in executive functioning, attention, and learning and memory within a few days following use, yet more recent work suggests that these impairments may not persist with longer-term abstinence. In addition, neuroimaging studies have identified functional brain changes that persist with abstinence, despite lacking performance decrements.

Marijuana in Adolescents

Despite the prevalence of marijuana use in adolescence, few studies have examined the neurocognitive impact of chronic marijuana use in adolescent samples. Heavy marijuana use has been associated with altered spatial working memory [31, 32], response perseveration [33], and memory [32, 34] functioning within a few days of use. Yet it is less clear whether these differences would persist with longer term abstinence. The following investigations were conducted with adolescent participants with at least 15 days of abstinence, allowing the differentiation of potentially persistent changes beyond the residual effects of recent use.

To address the question of persistent neurocognitive decrements in adolescent marijuana users, Schwartz and colleagues [35] conducted a prospective neuropsychological study. In an attempt to control for other substance use and lifestyle variables, marijuana-dependent youths and non-marijuana using polysubstance abusers were selected from an inpatient treatment program. Participants were 10 marijuana-dependent youths, 8 inpatient polysubstance using comparison teens who had limited experience with marijuana, and 9 community non-using control teens. All teens were 14 – 16 years old, had no history of heavy alcohol use or learning disabilities, and were not currently using any psychoactive medications. Neuropsychological functioning was assessed two to five days after admission to the treatment program, and again six weeks later. All three groups demonstrated similar overall verbal and performance IQ scores, but marijuana-dependent teens showed short-term memory deficits compared to other groups. At baseline testing, marijuana-dependent youths showed poorer performance of both immediate and delayed recall of visual and verbal information relative to drug abusing and non-using control youths. Further, marijuana users failed to show significant improvements in short term memory abilities following 6 weeks of abstinence. Thus, results indicate that marijuana may have long-term effects on short-term learning and memory in adolescents. Moreover, deficits were not observed in a group of polysubstance using youths with similar lifestyles as the marijuana users, suggesting a potential unique influence of marijuana on learning and memory. Yet it is unclear how other psychiatric or behavioral features may have contributed to results, and teens in this study were in a substance abuse treatment program, so may have differed from community marijuana users.

In an assessment of community youths, overall IQ was examined in 15 current heavy marijuana users who smoked at least 5 joints per week, 9 current light users who smoked fewer than 5 joints per week, 9 former users who had not used regularly for at least 3 months, and 37 non-users [36]. Participants were recruited from a larger study of neurocognitive functioning of youths prenatally exposed to marijuana or cigarettes. IQ was assessed at age 9 – 12, before substance use initiation, and again at age 17 – 21. Although baseline IQ did not differ between groups, current heavy users demonstrated lower IQ scores than non-users. Current heavy users had an average 4 point reduction in IQ between baseline and follow-up testing; although this is a modest decline, other groups demonstrated slight improvements in functioning. The current number of marijuana joints per week was negatively related to IQ difference score, with light users demonstrating no decrease in IQ between baseline and follow-up, while total lifetime exposure and duration of use were not related to IQ difference score. This could indicate that only relatively heavy use negatively impacts cognition, or that deficits associated with light use may be too subtle to detect with full scale IQ tests.

In a follow-up investigation with the same study design, more specific domains of neurocognitive functioning were examined in 19 current heavy marijuana users, 19 current light users, 16 former users, and 59 non-users [37]. Neuropsychological constructs were examined after controlling for baseline performance scores, obtained when participants were ages 9 – 12, demographics, cigarette and alcohol use, and psychiatric comorbidity. As detected previously, overall IQ was lower in current heavy marijuana users compared to non-users. In addition, heavy users performed more poorly than controls on tests of processing speed and immediate and delayed memory. Heavy users performed similarly as controls on tests of attention, working memory, abstraction, and vocabulary. Moreover, former users also showed similar performance as controls on all tests, suggesting that heavy marijuana use during adolescence may not be associated with permanent neurocognitive changes. By employing a longitudinal design, this study best controls for potential premorbid confounds. Importantly, participants from this study were part of an ongoing investigation of neurocognition in youths prenatally exposed to alcohol, nicotine, or marijuana. Although controlled for in analyses, prenatal exposure may have contributed abnormalities among marijuana users. Psychiatric disorders and other substance use may have also affected results, but were relatively well-matched between groups. Finally, it is unclear whether a longitudinal investigation of current users would also demonstrate recovery after extended abstinence, as in the former-user group. Nevertheless, this study provides compelling evidence of neurocognitive dysfunction among a representative sample of adolescent marijuana users, and potential recovery after three months of abstinence.

In a longitudinal neuropsychological study, substance use disordered youths were followed for 8 years after treatment [38]. Participants included 47 young adults with histories of substance use disorders (mean age 25 years) and 26 demographically similar controls (mean age 23 years). Initial neuropsychological evaluations were performed while substance use disordered youths were in treatment programs (mean age 16 years) with 3 weeks of verified abstinence. Over the next 8 years, youths received neuropsychological testing and substance involvement interviews at 7 time points, until participants were age 24 on average. Participants were excluded for recent substance use, including heavy alcohol use 30 days prior or marijuana use 48 hours before testing. At the 8-year follow up time point, those with histories of substance use disorders demonstrated poorer performance on tests of atten-

tion. In particular, heavier marijuana use throughout the 8-year testing interval predicted greater attention dysfunction at the 8-year follow up, particularly on tests of speeded psychomotor processing, above and beyond the effects of baseline attention functioning and testing experience. Importantly, this study suggests that continued heavy marijuana use into young adulthood is associated with a decline in attention functioning. Yet it is unclear how use of alcohol and other substances may have interacted with marijuana to influence neurocognition.

A few neuroimaging studies have begun to explore neurocognition *in vivo*. Brain response to working memory was examined in a community sample of adolescent marijuana users after one month of abstinence. In this pilot investigation, 7 marijuana users who also smoked cigarettes were compared to 7 tobacco smokers with limited marijuana exposure and 7 non-using controls [39]. Participants were age 17 on average. Urine toxicology screens at the time of scanning were negative for cannabinoid metabolites. During fMRI scanning, participants performed an auditory verbal working memory task that varied both working memory load (1-back and 2-back conditions) and selective attention task (binaural and dichotic stimulus presentation); functional imaging data analyses were restricted to the hippocampus bilaterally. In addition to fMRI scanning, a continuous performance task ascertained sustained attention, and a computerized word recognition task assessed selective and divided attention. Compared to nonsmoking controls, marijuana users performed less accurately on the continuous performance task and the verbal working memory task. There were no significant differences in performance between marijuana users and smokers on any task. fMRI analyses revealed that smokers and non-using controls demonstrated deactivation of the right hippocampus, whereas marijuana users failed to do so. Sample sizes were small and fMRI analyses were limited to the hippocampus, which may minimize potential group differences. Further, although users were tested after a reported one month of marijuana abstinence, urine toxicology screens obtained at testing could be negative for cannabinoid metabolites despite use in the previous month [40], making it difficult to verify abstinence. Regardless, this study provides preliminary evidence of impairments that persist beyond the effects of recent use.

In an extension of this work, Jacobsen and colleagues [41] further explored the neural underpinnings of verbal learning in 20 adolescent users of marijuana and tobacco and 25 adolescent users of tobacco alone. Participants ages 13 – 18 (average age 17 years) were free from psychiatric and neurological disorders, and had abstained from marijuana for at least 2 weeks prior to assessment. Teens performed a verbal list learning task after *ad libitum* smoking and again during nicotine withdrawal, 24 hours after last tobacco use. A subset of participants (15 marijuana users and 18 smoking comparison youths) underwent fMRI scanning during the same verbal working memory task described earlier [39]; data were analyzed to characterize overall brain functioning as well as the degree of functional connectivity between brain regions involved. Marijuana users demonstrated poorer verbal recall after a 25 minute delay than comparison youths during nicotine withdrawal, but not during the smoking condition. On the verbal working memory task, marijuana users showed a greater reduction in accuracy with increasing working memory load relative to comparison teens. During nicotine withdrawal, marijuana users showed increased activation relative to comparison youths in posterior brain regions when working memory load was high, suggesting increased neural effort in attempt to achieve task demands. Moreover, different patterns of frontoparietal functional connectivity under smoking and abstinence conditions were observed only in marijuana users, suggesting disrupted neurocircuitry associated with adolescent marijuana use. Neurocognitive abnormalities among marijuana users were observed during nicotine withdrawal but not during *ad libitum* smoking, indicating that nicotine use may mask the deficits associated with marijuana use. Yet it is unclear how these adolescents would compare to a group of non-users.

Our group has recently performed a series of studies examining neurocognitive functioning among a community sample of heavy marijuana users and controls, ages 16 – 18, after a month of monitored abstinence. Cannabinoid metabolites remain detectable in urine for at least four days [40] and 27 days on average in heavy using adults [17]. Therefore, abstinence was verified with biweekly urine toxicology screens for one month prior to neuropsychological and neuroimaging assessments. Groups were matched on demographics, and all teens were free from psychiatric comorbidity, history of neurological disorders, and psychotropic medication use. Marijuana users demonstrated greater alcohol, cigarette, and other drug (mostly oral opiates) use than controls, although such use was limited. Neuropsychological functioning was ascertained in 31 adolescent marijuana users and 34 non-using controls following $\geq$23 days of monitored abstinence [42]. Individual tests were divided into eight neuropsychological domains: psychomotor speed, complex attention, sequencing ability, verbal story memory, verbal list learning, visuospatial function and memory, verbal accuracy, and planning and problem solving. After controlling for alcohol use and depressive symptoms, abstinent adolescent marijuana users demonstrated poorer complex attention, sequencing ability, and verbal story memory, and slower psychomotor speed compared to controls. Moreover, greater lifetime marijuana use was associated with poorer performance in these cognitive domains, even after controlling for lifetime alcohol use.

A subset of these youths was included in structural and functional neuroimaging investigations. Overall brain white matter volume and left and right hippocampal volume were examined in relation to depressive symptoms among 16 marijuana users and 16 controls [43]. Although no participant met DSM-IV criteria for past or current mood disorder, marijuana users demonstrated greater levels of depressive symptoms than controls. No group differences in white matter or hippocampal volume were found, yet a negative relationship between white matter volume and depressive symptoms was found among marijuana users, but not among controls. The results could suggest that heavy marijuana use during youth may negatively impact mood by disrupting white matter pathways between frontal and limbic regions involved in mood regulation.

The functional influence of adolescent marijuana use was examined in-vivo in an fMRI study of inhibitory processing. fMRI scans were acquired as 16 28-day abstinent marijuana users and 17 controls performed a go/no-go task [44]. De-

spite similar task performance, marijuana users exhibited increased fMRI response during both inhibitory and non-inhibitory trials of the go/no-go task, particularly in dorsolateral prefrontal and parietal regions. Those with a later age of onset and briefer duration of regular use showed the greatest increase in brain response. This could indicate an inverted U-shaped pattern of activation, such that youths with relatively recent initiation show compensatory increases in activation, while those with more long-term use demonstrate neuroadaptive processes resulting in similar response patterns as controls.

In a related fMRI study of 15 28-day abstinent marijuana users and 17 controls, teens performed a spatial working memory task that contrasted 2-back location working memory with simple attention (dot detection) [45]. Relative to controls, marijuana users demonstrated reduced fMRI response to spatial working memory trials in right dorsolateral prefrontal cortex, and increased response in right posterior parietal cortex, despite equivalent behavioral performance between groups. During the attentional baseline condition, marijuana using teens showed greater response in occipital areas associated with visual attention. Together, these results are consistent with increased spatial rehearsal and visual attention processing subserved by parietal and occipital regions, but decreased use of frontally-mediated executive strategies among marijuana using teens, even after a month of abstinence.

Expanding on these findings, we examined the relationship between behavioral performance and fMRI response during spatial working memory among 17 28-day abstinent marijuana users and 17 non-using controls [46]. Interactions between task performance and group revealed a positive relationship between performance and brain response in left temporal regions and a negative relationship in right temporal regions among marijuana users, but the opposite relationships among controls. These results suggest that among marijuana users, those who recruit additional brain regions and utilize alternative, verbally-mediated strategies perform well, while those take a more traditional spatial approach demonstrate poorer performance.

These neuropsychological and neuroimaging studies provide evidence of alternative neural response patterns among marijuana using teenagers even after a month of verified abstinence. Biweekly urine toxicology screens verified abstinence, ensuring that results were not attributable to residual effects of recent use. However, in general, approximately one quarter of marijuana users who began the urine toxicology procedure was unable to maintain abstinence for a month before the neurocognitive assessments. Therefore, it is unclear whether the specific cognitive or motivational features involved in maintaining abstinence may have contributed to the observed cognitive performance and neural response patterns. Moreover, these studies only assessed participants following one month of abstinence, and it is unknown whether marijuana users and controls would have differed prior to the initiation of the abstinence period. Thus, it is unknown whether or not marijuana users improved in functioning throughout the first month of abstinence. Finally, most of the marijuana users in these studies were moderate to heavy drinkers. Although results remained significant after controlling for alcohol use, it is difficult to determine whether the observed findings may be partially related to interactive effects of alcohol and marijuana on the brain.

To address the issue of whether neural response patterns observed among abstinent users represent persisting changes, we performed a preliminary cross-sectional investigation comparing recent users to abstaining users [47]. Participants were 13 recent users (2 – 7 days abstinent), 13 abstinent users (27 – 60 days abstinent), and 18 non-using controls ages 15 – 18 who performed a spatial working memory task during fMRI acquisition. Recent users showed more fMRI response compared to abstinent users in medial and left superior prefrontal cortices, bilateral insula, and right superior parietal cortex, suggesting increased reliance on working memory updating, spatial rehearsal strategies, and inhibitory control. Although cross-sectional, these results suggest improvements in neurocognition during early abstinence from marijuana. However, longitudinal investigations are needed to characterize the potentially persisting effects and recovery process.

In summary, studies of adolescent marijuana users provide evidence of neurocognitive dysfunction within a few days of last use, but it is less clear whether or for what duration these deficits persist as abstinence continues, or how neurocognitive functioning recovers through different stages of sobriety. Among the relatively few studies of adolescents, continuous measures of abstinence duration were not significantly associated with levels of neurocognitive performance. The small sample sizes of most studies may mask measurable effects, particularly if most neural recovery occurs during the first week of abstinence [12]. Neuropsychological and neuroimaging studies have identified abnormalities up to a six weeks following use (Table **1**). After an abstinence period of at least 6 weeks (average of 10 months), marijuana users recruited from the community demonstrated attention and verbal working memory deficits, along with fMRI abnormalities [39]. Within a treatment sample, longitudinal evidence similarly suggests learning and memory impairments at least 6 weeks following use, although slight improvement was noted [35]. Cross-sectional evidence suggests that although IQ, memory, and processing speed impairments were observed among marijuana users with exposure as recently as the day before testing, no deficits were found among a group of marijuana users who had discontinued heavy use at least 3 months prior [36, 37]. Thus, while adult research indicates neurocognitive recovery within 4 weeks of discontinuation [12], adolescent investigations point to potential alterations up to 6 weeks following last use, but raise the possibility of normalization after 3 months. Longitudinal investigations at different durations of abstinence will help characterize the timeline of neurocognitive recovery among teens who discontinue use, and help articulate the neuroanatomical and functional changes associated with such improvements.

The neuroimaging studies reviewed have identified abnormalities in brain functioning among adolescent marijuana users, yet the implications of altered activation warrant consideration. In general, adolescent marijuana users perform well on easier tasks, such as those with low working memory load, but show evidence of decrements on more difficult tasks and demonstrate different patterns of neural activation than non-users [41, 45]. This may suggest that on easier

Table 1. Neuropsychological and Imaging Studies of Brain Functioning in Human Adolescent Marijuana Users at Increasing Durations of Abstinence

Study	Age of Users	Marijuana Users	Non-Abusing Controls	Other Groups	Length of Abstinence		Impairments in Marijuana Users
	M ± *SD*	*n*	*n*	*n*	Minimum	Average	
Jacobsen *et al*., 2007 [41]	17.3 ± 1.1	20	none	25 cigarette smokers	15 days	4.8 months	verbal recall, verbal working memory, verbal working memory fMRI abnormalities
Medina *et al*., 2007a [42]	18.2 ± 0.9	31	34	none	23 days	Unknown	Psychomotor speed, attention, verbal story memory
Medina *et al*., 2007b [43]	18.0 ± 0.7	16	16	none	28 days	Unknown	Negative relationship between white matter volume and depressive symptoms
Tapert *et al*., 2007 [44]	18.1 ± 0.7	16	17	none	28 days	58.4 days	go/no-go fMRI abnormalities; sequencing errors on DKEFS Trails, intrusions on word list learning
Schweinsburg *et al*., in press [45]	18.1 ± 0.7	15	17	none	28 days	60.4 days	Spatial working memory fMRI abnormalities
Padula *et al*., in press [46]	18.1 ± 0.8	17	17	none	28 days	Unknown	Altered relationships between spatial working memory task performance and fMRI response
Jacobsen *et al*., 2004 [39]	17.4 ± 1.0	7	7	7 cigarette smokers	1.5 months	10 months	attention, verbal working memory, verbal working memory fMRI abnormalities
Schwartz *et al*., 1989 [35]	Range: 14 – 16	10	9	8 polysubstance users	6 weeks	Unknown	learning & memory
Fried *et al*., 2005 [37]	17.8 ± 0.8	19	59	19 light users	1 day	Unknown	IQ, processing speed, memory
	17.9 ± 1.1	16	59	19 light users	3 months	Unknown	No NP deficits

Abbreviations: NP, neuropsychological; fMRI, functional magnetic resonance imaging; DKEFS, Delis-Kaplan Executive Function System.

tasks, marijuana users are able to utilize alternate strategies, and perhaps increase neural recruitment to maintain performance. Yet on more difficult tasks, these alternate strategies may be less effective for the cognitive demands, leading to performance impairments. In addition, attention dysfunction associated with marijuana use has been implicated in adult as well as adolescent studies, and could underlie difficulty in other cognitive domains. When attention demands are low, resources can be recruited and divided efficiently, leading to adequate performance. Thus, tasks utilized to purely test attention skills may not be sufficiently difficult to elicit impaired performance among marijuana users. However, tasks with greater working memory load or requiring stronger executive response components may also require alternate selection and division of attention that marijuana users are less able to employ. Thus, neuroimaging task refinements will help elucidate the specific subcomponents of attention, working memory, and learning and memory that may be most affected in adolescent marijuana users.

2. ARE ADOLESCENTS MORE VULNERABLE THAN ADULTS?

Given the continued neurodevelopment throughout adolescence, adolescents may be more vulnerable than adults to certain neural consequences of heavy marijuana use. Developmental changes occur on different trajectories in various brain regions, and consequently, each region may have specific periods of heightened vulnerability to insult as development progresses. Alternatively, the adolescent brain may have greater resiliency capacity during this remodeling pe-

riod, allowing for more complete recovery of functioning if marijuana use is discontinued early. A brief discussion of neurodevelopment is needed before attempting to determine how the pattern of deficits among adolescents may differ from that in adults.

Adolescent Neurodevelopment

While development of overall brain size is largely complete by age 5 [48], specific structural and functional changes continue into adolescence, leading to greater cognitive efficiency. Gray matter volumes decrease, in part due to synaptic pruning as unnecessary neural connections are eliminated [48-50], and white matter volumes increase as myelination progresses [48, 51]. A recent longitudinal study revealed region-specific rates of structural maturation, with late development of higher-order association cortices, including superior parietal, superior temporal, and prefrontal regions [52], underlying maturation of visuospatial, attention, memory, and executive functioning skills throughout adolescence [53, 54]. Consequently, these higher order constructs may be most impacted by adolescent marijuana use.

Maturing neurotransmitter systems may also influence sensitivity to marijuana in adolescence as well. The psychoactive effects of marijuana are exerted primarily through the interaction of THC with cannabinoid (CB)1 receptors in the brain, which are most densely located in the basal ganglia, hippocampus, cerebellum, and association cortices, including prefrontal cortex and cingulate gyrus [55-57]. Consequently, the cognitive processes subserved by these brain regions may be most affected by early chronic cannabinoid use. Further, the cananbinoid receptor system develops relatively late [58], and receptor densities in these regions peak during adolescence among rats [59], potentially increasing sensitivity to cannabinoid effects during adolescence.

Gender differences in the rate and timing of neurodevelopment unfold over the course of adolescence. In particular, frontal, parietal, and temporal lobe gray matter volumes peak earlier in girls than in boys, and greater age-related increases in white matter are seen among males [60]. The amygdala and hippocampus, demonstrate sexually dimorphic rates of development as well: the amygdala, which is dense with androgen receptors, increases in volume only in males, while the estrogen-rich hippocampus increases in volume among females [61]. Gender differences in CB1 receptor binding and interactions between cannabinoids and sex hormones have also been observed [59, 62], raising the possibility of gender differences in neural response to cannabinoids. Given the gender differences in neurodevelopment as well as potential cannabinoid influence, it is possible that boys and girls may be differentially affected by chronic marijuana use during adolescence.

Rodent Models of Adolescent Vulnerability

Animal models provide a unique opportunity to directly determine whether marijuana is related to greater impairments in adolescents than adults. Rodent studies have the ability to control premorbid and environmental factors, as well as to directly administer cannabinoids during adolescence. However, animal models do not generalize fully to humans, and abilities such as verbal learning cannot be studied. In addition, dose scheduling and synthetic cannabinoid administration may not be comparable to human use patterns. In particular, natural marijuana contains many cannabinoids; although THC is the main active constituent, it may interact with other plant cannabinoids to produce effects unique to natural marijuana that cannot be replicated with an isolated or synthetic cannabinoid. Despite these limitations, rodent studies offer preliminary evidence of the unique cognitive effects of cannabinoid use in adolescents compared to adults.

The question of adolescent vulnerability was first addressed in rat studies over 20 years ago. A series of studies examined different aspects of learning in rats after chronic cannabinoid administration. Rats received an oral preparation of a natural marijuana extract dosing THC at 20mg/kg per day, suggested as comparable to moderate use in humans. In initial studies, cannabinoid treatment began when rats were immature, approximately 30 – 40 days old, and lasted for 3 – 6 months. At least one month after drug discontinuation, animals were trained and tested on learning tasks. Compared to placebo-treated control rats, marijuana-treated rats demonstrated impairments on maze learning [63, 64] and a differential reinforcement of low- rate responding task [65], and facilitated active avoidance learning on a shuttle-box task [66]. The authors note that these results are similar to findings among rats with hippocampal lesions [66], and suggest learning dysfunction associated with chronic marijuana administration. In a final experiment, marijuana extract was administered to a group of mature rats, aged about 70 days at initial drug treatment [67]. Following similar procedures as the previous studies, a daily oral dose of THC at 20 mg/kg was administered for 3 months, and behavioral training began one month after drug discontinuation. In contrast to previous findings among rats exposed when immature, adult-exposed rats did not show impaired performance on maze learning or the differential reinforcement of low-rate responding task, and facilitation of shuttle box avoidance learning was less marked. Together, these results indicate a greater vulnerability to learning impairments when chronic marijuana exposure occurs during adolescence, and limited cognitive dysfunction when marijuana exposure occurs among mature animals [67]. Further, lighter THC doses of 10 mg/kg did not produce significant learning impairments [63], suggesting that only heavy marijuana use is associated with learning deficits in adolescents.

More recently, prepulse inhibition, object recognition, and motivation were examined among rats that had received chronic treatment with the synthetic cannabinoid agonist WIN 55,212-2 either as adolescents or adults [68]. Adolescent treatment began at 40 days of age, while adult treatment began at 70 days. Cannabinoid treatment consisted of 20 injections over the course of 25 days; drug injections were administered irregularly to mimic use patterns in humans. Behavioral testing began 10 days following drug discontinuation. Compared to control rats, adolescent-treated rats showed disrupted prepulse inhibition of the acoustic startle response, suggesting dysfunctional preattentive filtering of sensory information, impaired object recognition, and lower break point on a progressive ratio task, indicating reduced motivation. In contrast, rats receiving cannabinoid administration as adults demonstrated no behavioral deficits, suggesting increased vulnerability to cannabinoid-induced functional impairments among adolescent rats.

Another group identified gender-specific effects of chronic adolescent cannabinoid exposure [69, 70]. Female and male rats were examined in separate studies utilizing similar procedures. The cannabinoid agonist CP 55,940 was administered to adolescents aged 30 days and adults aged 56 days at treatment initiation. Rats received increasing cannabinoid doses for 21 consecutive days, and behavioral assessments began 22 – 28 days following final drug exposure. Among females, cannabinoid-treated adolescent, but not adult, rats demonstrated impaired working memory on an object recognition task compared to vehicle-treated controls [70]. Interestingly, among males, cannabinoid treatment during adolescence and adulthood produced similar working memory deficits [69]. Thus, among females, adolescents may be more susceptible and adults more resilient to long-lasting cannabinoid-induced neural injury, whereas in males, both adolescents and adults are equally vulnerable.

Developmental sensitivity to cannabinoids was further examined in a study assessing learning following acute and chronic THC exposure in male rats [71]. Beginning at age 30 – 32 days for adolescents and 65 – 70 days for adults, an injection of 5 mg THC/kg was administered for 21 consecutive days. After a 28-day drug-free period, animals were trained on both spatial and non-spatial versions of a water maze task. The same tasks were used to ascertain the acute effects of varying doses of THC among adolescent and adult rats. Acute THC exposure led to greater learning impairments on both the spatial and non-spatial tasks in adolescents than in adults. Conversely, following chronic drug administration, neither animals treated as adolescents nor as adults demonstrated maze-learning impairments relative to vehicle-treated controls. Thus, while adolescents may be more sensitive to the acute effects of cannabinoids, both adolescents and adults demonstrate similar recovery of functioning following discontinuation of chronic treatment. However, the THC dose of 5mg/kg, which was light relative to other studies demonstrating impairment, may not have been heavy enough to produce lasting changes [63].

The influence of adolescent cannabinoid exposure on memory functioning was again examined in a recent investigation of behavior and hippocampal microstructure [72]. Adolescent rats were 32 days old, and adults were 64 days old when chronic THC administration began. Rats were given a priming dose of 1mg/kg THC for two days, then received eight total doses of 5mg/kg THC that were administered every other day. A novel object recognition task was given 10 days following THC exposure, and protein expression in the hippocampus was examined after 17 days of abstinence. Object recognition memory was impaired only in THC-exposed adolescent rats, but not in adults. Further, THC exposure was associated with greater abnormalities in hippocampal protein expression in adolescents than in adults. Together, these results provide structural and behavioral evidence of adolescent vulnerability to cannabinoid-induced memory impairments.

In general, these rodent studies point to increased susceptibility to persistent cognitive impact of cannabinoid exposure among adolescents relative to adults, particularly in the domains of learning and memory and working memory. These effects were observed at relatively high doses of cannabinoids that may not be comparable to typical human consumption by a heavy user. Additional animal studies might attempt to examine effects at varying doses, particularly with natural marijuana extracts, as well as characterizing performance in other cognitive domains that appear affected by marijuana use in humans, such as attention.

Human Studies of Adolescent Vulnerability

A few human studies have begun to address the issue of adolescent vulnerability by studying heavy marijuana using adults who initiated use early in adolescence.

In an extension of their previous study [12], Pope and colleagues [73] ascertained neuropsychological functioning among current and former heavy marijuana users and non-abusing controls after 28 days of monitored abstinence. All subjects were free from current psychiatric disorders including alcohol dependence, psychotropic medication use, significant head injury or medical disorders. Marijuana users were separated into 69 subjects who began using marijuana before age 17, and 53 participants who began use at age 17 or after. After controlling for age, gender, ethnicity, and family background, later-onset users were not significantly different from controls on any cognitive measure. However, early-onset users demonstrated poorer performance than controls on tests of verbal abilities, including estimated verbal IQ, memory of verbal lists, and use of semantic categories. Verbal IQ, based on the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised [74], generally remains stable over time and is resilient to neural injury [75], therefore providing an estimate of cognitive functioning before the onset of marijuana use. Thus, the authors suggest that lower verbal IQ scores among early-onset users may reflect poorer overall functioning predating the initiation marijuana use. After controlling for verbal IQ, verbal decrements among early-onset users no longer remained significant, suggesting that neuropsychological impairments associated with early initiation of marijuana use may be accounted for by lower overall premorbid cognitive ability, rather effects directly related to marijuana use. Alternatively, lower verbal IQ scores among early-onset users may be attributable to lower educational attainment. Youths who initiate marijuana use at an early age may perform more poorly in school because of cognitive, social, and psychological influences, including limited attentional capacity, reduced school attendance, or lack of motivation [76]. Together, these factors could contribute to youths' attenuated vocabulary acquisition, and therefore lower verbal IQ.

Neural functioning was examined among 17 young adult marijuana users and 16 controls in an electrophysiological study of visual processing [77]. All participants were free from medical and psychiatric disorders, including alcohol dependence, and had minimal experience with drugs other than marijuana. Marijuana users reported use within the past week, but were abstinent for at least 24 hours before testing. Subjects underwent steady state visual evoked potential recordings while viewing flickering white squares on a black background. Neuropsychological testing revealed no differences between marijuana users and controls, yet marijuana users demonstrated aberrant steady state visual evoked potentials. In particular, age of onset of marijuana use was related to neural response, such that participants who initiated use at an earlier age showed larger abnormalities. Interest-

ingly, female marijuana users showed greater alterations than male users. This study provides evidence of altered sensory functioning among heavy marijuana users, particularly those who started at a younger age, yet abnormal steady state visual evoked potentials may be related to attention dysfunction. Further, the results suggest a potential gender difference in the neural impact of marijuana use.

Ehrenreich and colleagues [78] examined additional aspects of visual functioning, including visual scanning, attention shifting, and working memory in a group of young adults comprising 99 regular marijuana users and 49 non-using controls. Regression analyses revealed that an earlier age of onset of marijuana use was negatively associated with visual scanning reaction times, while current cannabinoid metabolite levels, age, and lifetime exposure were not. When grouped based on age of onset, those who began using before age 16 demonstrated significant slowing on visual scanning reaction times, whereas those who began using at age 16 or later performed similarly as controls. Further, regardless of age of onset, marijuana users were not impaired on tests of attentional flexibility or working memory, indicating attentional dysfunction specific to visual scanning among early onset users. Of note, visual scanning speed typically improves in early adolescence, and these brain regions may be particularly influenced by marijuana; consequently, marijuana exposure may lead to persisting impairments in visual scanning abilities for those who used during this sensitive period of neuromaturation. While plausible, all participants in this study had used marijuana within one week of testing, and the minimum time since last use was only two hours. Thus, visual scanning abnormalities may be related to residual effects of recent use, or even to the acute effects of current intoxication among those who used several hours prior to testing.

The influence of early marijuana use on electrophysiological functioning was further examined in an event-related potential study of auditory selective attention in young adult marijuana users and non-using controls, all of whom were free of medical or psychiatric disorders [79]. Marijuana users consisted of 10 individuals who initiated use before age 16 and 11 individuals who began at age 16 or later; comparison subjects were 13 demographically similar non-users. Event-related potentials were recorded while participants were attempted to identify target tones based on location, pitch, and duration of presented stimuli. In frontal lobe regions, controls exhibited a shorter latency negative component to target tones relative to non-targets, whereas marijuana users did not demonstrate this pattern. Marijuana users also displayed reduced P300 amplitudes to target tones. Moreover, early-onset users evidenced a greater degree of neurophysiological dysfunction than late-onset users. However, data on age of onset should be interpreted with caution, as early-onset users had more years of regular marijuana use and more frequent past-month use than late-onset users. Although years of regular use and cannabinoid metabolite levels were not significantly associated with electrophysiological indices, it is possible that group differences were related to these use characteristics rather than age of first use. This is particularly important in terms of frequency of recent use, since marijuana-related neurocognitive abnormalities may be accounted for by residual drug effects following recent heavy use [12, 16]. In addition, although not statistically different, the late-onset group consisted of 90% males, while the early-onset group had only 50% males; this gender imbalance may contribute to group differences between early and late onset users. Nevertheless, the results of this study suggest that marijuana users exhibit different attentional allocation and implement less effective strategies than controls, and that earlier exposure to cannabinoids may lead to increased risk of neural dysfunction later in life.

Additional measures of brain functioning were ascertained in a study of brain morphology and global cerebral blood flow in 29 marijuana users who initiated use before age 17, and marijuana users who began use at age 17 or later [80]. Participants were free from psychiatric, medical, or neurological disorders, were not currently using medications or large amounts of alcohol, and were matched on demographic characteristics. Gray matter, white matter, and ventricular volume were calculated as a percent of overall brain volume. Regional gray matter volumes, whole-brain white matter volumes, and global cerebral blood flow were examined for main effects and interaction of age of onset and gender. Although no measure of gray matter, white matter, or cerebral blood flow was associated with duration of marijuana use, several relationships to age of marijuana initiation were observed. Overall gray matter volumes were smaller in early-onset users compared to late-onset users. Regional analyses revealed that this difference was greatest in the frontal and parietal lobes, while gray matter volumes in subcortical regions and the hippocampus and amygdala were not related to age of onset. Early-onset users displayed larger whole brain white matter volumes. Global cerebral blood flow was higher in early-onset males compared to late-onset males, yet this difference was not observed in females. This study provides interesting insight into structural and functional brain differences between marijuana users who began in early adolescence compared to those who began later. Unfortunately, the results are difficult to interpret given the lack of non-using control group. It is unclear whether the smaller gray matter volumes and larger white matter volumes displayed by the early-onset users are more or less aberrant than volumes displayed by late-onset users, or whether either group would significantly differ from a group of matched non-users. Moreover, the significance of these volumetric differences is unknown, since no measures of behavioral, psychological, social, or cognitive functioning were examined. Of particular interest, however, is the finding of cerebral blood flow differences between early and late onset males, but not females. Although the functional significance of such blood flow differences is unclear, yet this result provides evidence of potential gender differences in the neural impact of marijuana exposure.

Overall, these studies consistently indicate that adults who initiated regular marijuana use earlier in adolescence demonstrate greater abnormalities than those who began to use marijuana later, particularly during visual attention tasks (Table **2**). In addition, individuals who began use later in adolescence demonstrated few impairments. Together, these results support a greater vulnerability to neurocognitive dysfunction associated with marijuana use in early adolescence. Deficits in verbal skills were observed in a large sample of early-onset users even after 28 days of abstinence, suggesting persisting effects that are not observed in late-onset users [73]. Results of these studies must be considered carefully, however. Visual atten-

Table 2. Studies Examining Age of Onset of Cannabis Use on Brain Functioning in Adult Human Users

Study	Marijuana Users		Non-Abusing Controls	Minimum Length of Abstinence	Results for Early Onset Relative to Late Onset
	Early Onset Age of Onset; *n*	Late Onset Age of Onset; *n*	*n*		
Ehrenreich *et al*., 1999 [78]	<16 years; 48	≥16 years; 51	49	2 hours	↓ visual scanning
Kempel *et al*., 2003 [79]	<16 years; 10	≥16 years; 11	13	24 hours	↓ selective attention brain waves
Skosnik *et al*., 2005[a] [77]	Mean age onset: 15.9 males, 15.1 females; *n* = 17		16	24 hours	↓ visual processing brain waves
Wilson *et al*., 2000 [80]	<17 years; 29	≥17 years; 28	none	2 weeks	↓ gray matter, ↑ white matter; EO males: ↓ blood flow
Pope *et al*., 2003 [73]	<17 years; 69	≥17 years; 53	87	28 days	↓ verbal IQ, ↓ verbal recall, ↓ semantic categories

[a]Age of onset examined only as a continuous variable.

tion abnormalities were observed after very recent use among most participants, and it is unclear whether deficits would persist longer. Verbal skill deficiencies may be related to inferior academic achievement or poorer premorbid intellectual abilities among early-onset marijuana users, rather than a direct neural impact of marijuana. Yet despite the limitations in interpreting these studies, together they offer consistent evidence of greater neurocognitive deficits among marijuana users who initiated use early in adolescence, and suggest that the adolescent brain may be particularly vulnerable to the influence of heavy marijuana use.

DISCUSSION

After reviewing the literature, there is preliminary evidence of persisting neurocognitive abnormalities among adolescent marijuana users. Subtle deficits in learning and memory, working memory, and attention have been observed in heavy using youths at least 6 weeks following cessation of use, although these impairments may not last as long as 3 months after discontinuation. In addition, it appears that adolescents are more vulnerable to the neural impact of heavy marijuana use than adults. Animal research and studies of human adults support the conclusion that those who begin at an earlier age show greater dysfunction than late-onset users. Importantly, no study demonstrated improved performance among marijuana users, or among early-onset users relative to late-onset users, indicating a disruptive effect of cannabinoids. In addition, lighter use was not always associated with neurocognitive decrements in humans [36, 37] or animals [63], suggesting that impairments may be related to heavier use. Taken together, the studies reviewed suggest that adolescents who persist in frequent marijuana use may be at risk for persistent neurocognitive abnormalities.

Although adolescents who use marijuana heavily demonstrate decrements compared to non-using teens, it is still unknown whether marijuana use caused or contributed to these effects. In most cases, decrements were observed among those with relatively heavy, regular marijuana use. Lighter use, even if chronic, was often not associated with neurocognitive dysfunction. Thus, it is unclear whether only very heavy use is detrimental to brain functioning, or whether very heavy users differ from lighter users on other factors that account for abnormalities. In their longitudinal studies, Fried and colleagues assessed both marijuana users and non-users before the onset of substance use; despite similar premorbid intellectual functioning, current heavy marijuana users demonstrated impairments compared to non-users [36, 37]. However, other pre-existing factors that weren't measured may have contributed to cognitive differences between groups. For instance, the types of youths who initiate heavy marijuana use at a young age may perform more poorly in school because of social, cognitive, and motivational factors that continue to affect social and occupational attainment into adulthood, which in turn may contribute to neurocognitive differences. Moreover, both animal and human studies have indicated an association between heavy marijuana use and behavioral features such as increased anxiety, affective, and psychotic symptoms [81-85], particularly among those who may have pre-existing vulnerabilities [84]. Interactions between genes, the environment, and such behavioral factors may influence marijuana use and neurocognition. Although beyond the scope of this review, future studies should attempt to identify the possible premorbid features that contribute to neurocognitive abnormalities among adolescent marijuana users.

In addition, the mechanism of adolescent vulnerability to the neural impact of marijuana is unresolved. The adolescent brain may be susceptible to damage due to continued neuromaturation, including peak sensitivity to cannabinoid receptor interactions. Yet other factors associated with adolescence, including changing hormone levels during puberty, altered sleep patterns, increased sensation-seeking and risky behaviors, and changing social environments may contribute to both changes in neural functioning as well as vulnerability to marijuana use effects. Future investigations might attempt to understand the basis of this adolescent vulnerability.

Given that many marijuana users have experience with alcohol, nicotine, and other drugs [86], it is difficult to disentangle the unique influence of marijuana. Importantly, adolescents with alcohol use disorders demonstrate functional brain abnormalities [87], and even moderate alcohol use may impact neural functioning [88]. Yet the inclusion of marijuana users with other substance use histories maintains representativeness in the sample, allowing for better generalization to the population of adolescent marijuana users. Most of the studies of adolescent participants attempted to control for alcohol other substance use among marijuana users by either including a com-

parison group with similar substance use patterns or by covarying for substance use in analyses. Future studies might attempt to ascertain the impact of alcohol and other drug use among marijuana users by contrasting pure marijuana users with those with other substance use experience.

Gender differences in the neural impact of marijuana use have rarely been explored, but provide an intriguing line for future research. Among adult users, women demonstrated greater neural abnormalities in visual processing [77]. Marijuana-exposed female adolescent rats were more vulnerable to learning deficits than adult females, but male adolescents and adults showed similar impairments [69, 70], again pointing to possible gender differences in the impact of marijuana use. Finally, among males, early onset users showed reduced cerebral blood flow compared to late onset users, yet this pattern was not observed among female marijuana users. Sex hormones may interact with marijuana, altering its effects and differentially impacting males and females. In particular, changes in cannabinoid effects have been observed throughout the estrous cycle, and gonadectomy alters cannabinoid receptor density [62]. Moreover, neuromaturation occurs earlier in females than males, particularly in frontal and parietal brain regions [60], which could underlie different effects of marijuana between male and female adolescents.

CONCLUSIONS

In sum, this review demonstrates that adolescent marijuana users show working memory, attention, and learning abnormalities that persist at least 6 weeks following cessation of use, but that these deficits may resolve with longer term abstinence. In addition, adolescent marijuana users may be more vulnerable to neural dysfunction than adults, yet the mechanism of this susceptibility remains unclear. Future investigations might disentangle the influence of psychiatric comorbidity and other substance use, as well as differentiate the component processes of working memory, attention, and learning that are most affected. Finally, attempts should be made to characterize the preexisting factors that may influence neural functioning in marijuana users. Although more studies are needed, the literature provides preliminary evidence for neurocognitive deficits associated with heavy marijuana use in adolescence, and may have implications for teens' future functioning.

Key Learning Objectives:

- To determine whether adolescent marijuana use is associated with persistent effects on neurocognition.
- To determine whether adolescents are more vulnerable to the neural influence of marijuana use than adults.

Future Research Directions:

- Longitudinal studies assessing neurocognition at different lengths of abstinence will determine the timeline of neurocognitive recovery among teens who discontinue marijuana use, as well as the potential preexisting differences among marijuana users.
- Studies with varied participants are needed to disentangle the influence of marijuana use from the influence of other substance use and psychiatric symptoms.
- The component processes of working memory, learning and memory, and attention that are most influenced by adolescent marijuana use should be examined in detail.

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REFERENCES

[1] SAMHSA. Results from the 2005 National Survey on Drug Use and Health: National Findings. Rockville, MD: Office of Applied Studies; 2006. Report No.; DHHS Publication No. SMA 06-4194.

[2] Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. The Monitoring the Future national survey results on adolescent drug use: Overview of key findings, 2005. Bethesda, MD: National Institute on Drug Abuse; 2006.

[3] Stinson FS, Ruan WJ, Pickering R, Grant BF. Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. Psychol Med 2006; 1-14.

[4] Tims FM, Dennis ML, Hamilton N, *et al*. Characteristics and problems of 600 adolescent cannabis abusers in outpatient treatment. Addiction 2002; 97(Suppl. 1): 46-57.

[5] Croft RJ, Mackay AJ, Mills AT, Gruzelier JG. The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology (Berl) 2001; 153: 373-9.

[6] Pope HG Jr., Jacobs A, Mialet JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. Psychother Psychosom 1997; 66: 179-84.

[7] Pope HG Jr., Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA 1996; 275: 521-7.

[8] Solowij N, Grenyer BF. Are the adverse consequences of cannabis use age-dependent? Addiction 2002; 97: 1083-6.

[9] Varma VK, Malhotra AK, Dang R, Das K, Nehra R. Cannabis and cognitive functions: a prospective study. Drug Alcohol Depend 1988; 21: 147-52.

[10] Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. Neurology 2002; 59: 1337-43.

[11] Lyons MJ, Bar JL, Panizzon MS, *et al*. Neuropsychological consequences of regular marijuana use: a twin study. Psych Med 2004; 34: 1239 - 50.

[12] Pope HG, Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001; 58: 909-15.

[13] Pope HG, Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Cognitive measures in long-term cannabis users. J Clin Pharmacol 2002; 42: 41S-7S.

[14] Carlin AS, Trupin EW. The effect of long-term chronic marijuana use on neuropsychological functioning. Int J Addict 1977; 12: 617-24.

[15] Schaeffer J, Andrysiak T, Ungerleider JT. Cognition and long-term use of ganja (Cannabis). Science 1981; 213: 465-6.

[16] Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 2003; 9: 679-89.

[17] Ellis GM, Jr., Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin Pharmacol Ther 1985; 38: 572-8.

[18] Pope HG, Jr., Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. Drug Alcohol Depend 1995; 38: 25-34.

[19] Struve FA, Straumanis JJ, Patrick G, Leavitt J, Manno JE, Manno BR. Topographic quantitative EEG sequelae of chronic marihuana use: a replication using medically and psychiatrically screened normal subjects. Drug Alcohol Depend 1999; 56: 167-79.

[20] Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. Pharmacol Biochem Behav 1991; 40: 683-8.

[21] Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. Biol Psychiatry 1995; 37: 731-9.

[22] Volkow ND, Gillespie H, Mullani N, *et al*. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res 1996; 67: 29-38.

[23] Block RI, O'Leary DS, Hichwa RD, *et al*. Cerebellar hypoactivity in frequent marijuana users. Neuroreport 2000; 11: 749-53.

[24] Loeber RT, Yurgelun-Todd DA. Human neuroimaging of acute and chronic marijuana use: Implications for frontocerebeller dysfunction. Hum Psychopharmacol Clin Exp 1999; 14: 291-304.

[25] Lundqvist T, Jonsson S, Warkentin S. Frontal lobe dysfunction in long-term cannabis users. Neurotoxicol Teratol 2001; 23: 437-43.

[26] Block RI, O'Leary DS, Hichwa RD, *et al*. Effects of frequent marijuana use on memory-related regional cerebral blood flow. Pharmacol Biochem Behav 2002; 72: 237-50.

[27] Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology (Berl) 2004; 176: 239-47.

[28] Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. Psychopharmacology (Berl) 2006; 185: 358-68.

[29] Gruber SA, Yurgelun-Todd DA. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. Brain Res Cogn Brain Res 2005; 23: 107-18.

[30] Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 2006; 129: 1096-112.

[31] Schweinsburg AD, Schweinsburg BC, Cheung EH, Brown GG, Brown SA, Tapert SF. fMRI response to spatial working memory in adolescents with comorbid marijuana and alcohol use disorders. Drug Alcohol Depend 2005; 79: 201 - 10.

[32] Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev 2007; 26: 309-19.

[33] Lane SD, Cherek DR, Tcheremissine OV, Steinberg JL, Sharon JL. Response perseveration and adaptation in heavy marijuana-smoking adolescents. Addict Behav 2007; 32: 977-90.

[34] Millsaps CL, Azrin RL, Mittenberg W. Neuropsychological effects of chronic cannabis use on the memory and intelligence of adolescents. J Child Adolescent Subst Abuse 1994; 3: 47-55.

[35] Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. Am J Dis Child 1989; 143: 1214-9.

[36] Fried P, Watkinson B, James D, Gray R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. CMAJ 2002; 166: 887-91.

[37] Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana--a comparison with pre-drug performance. Neurotoxicol Teratol 2005; 27: 231-9.

[38] Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. J Int Neuropsychol Soc 2002; 8: 873-83.

[39] Jacobsen LK, Mencl WE, Westerveld M, Pugh KR. Impact of cannabis use on brain function in adolescents. Ann NY Acad Sci 2004; 1021: 384-90.

[40] Fraser AD, Coffin L, Worth D. Drug and chemical metabolites in clinical toxicology investigations: the importance of ethylene glycol, methanol and cannabinoid metabolite analyses. Clin Biochem 2002; 35: 501-11.

[41] Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE. Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol Psychiatry 2007; 61: 31-40.

[42] Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc 2007; 13: 807-20.

[43] Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF. Depressive symptoms in adolescents: associations with white matter volume and marijuana use. J Child Psychol Psychiatry 2007; 48: 592-600.

[44] Tapert SF, Schweinsburg AD, Drummond SP, *et al*. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology (Berl) 2007; 194: 173-183.

[45] Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. Psychiatry Res, In press.

[46] Padula CB, Schweinsburg AD, Tapert SF. Spatial working memory performance and fMRI activation interactions in abstinent adolescent marijuana users. Psychol Addict Behav, In press.

[47] Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF. The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users submitted.

[48] Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H. Anatomical MRI of the developing human brain: what have we learned? J Am Acad Child Adolesc Psychiatry 2001; 40: 1012-20.

[49] Huttenlocher PR. Morphometric study of human cerebral cortex development. Neuropsychologia 1990; 28: 517-27.

[50] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997; 387: 167-78.

[51] Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 2001; 54: 255-66.

[52] Gogtay N, Giedd JN, Lusk L, *et al*. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci USA 2004; 101: 8174-9.

[53] Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. Biol Psych 2000; 54: 241-57.

[54] Sowell ER, Delis D, Stiles J, Jernigan TL. Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. J Int Neuropsychol Soc 2001; 7: 312-22.

[55] Eggan SM, Lewis DA. Immunocytochemical Distribution of the Cannabinoid CB1 Receptor in the Primate Neocortex: A Regional and Laminar Analysis. Cereb Cortex 2006.

[56] Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 1997; 77: 299-318.

[57] Herkenham M, Lynn AB, Little MD, *et al*. Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 1990; 87: 1932-6.

[58] Biegon A, Kerman IA. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human brain. Neuroimage 2001; 14: 1463-8.

[59] Rodriguez de Fonseca F, Ramos JA, Bonnin A, Fernandez-Ruiz JJ. Presence of cannabinoid binding sites in the brain from early postnatal ages. Neuroreport 1993; 4: 135-8.

[60] Giedd JN, Blumenthal J, Jeffries NO, *et al*. Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 1999; 2: 861-3.

[61] Giedd JN, Clasen LS, Lenroot R, *et al*. Puberty-related influences on brain development. Mol Cell Endocrinol 2006; 254-255: 154-62.

[62] Rodriguez de Fonseca F, Cebeira M, Ramos JA, Martin M, Fernandez-Ruiz JJ. Cannabinoid receptors in rat brain areas: sexual differences, fluctuations during estrous cycle and changes after gonadectomy and sex steroid replacement. Life Sci 1994; 54: 159-70.

[63] Fehr KA, Kalant H, LeBlanc AE. Residual learning deficit after heavy exposure to cannabis or alcohol in rats. Science 1976; 192: 1249-51.

[64] Stiglick A, Kalant H. Learning impairment in the radial-arm maze following prolonged cannabis treatment in rats. Psychopharmacology (Berl) 1982; 77: 117-23.

[65] Stiglick A, Kalant H. Residual effects of prolonged cannabis administration on exploration and DRL performance in rats. Psychopharmacology (Berl) 1982; 77: 124-8.

[66] Stiglick A, Llewellyn ME, Kalant H. Residual effects of prolonged cannabis treatment on shuttle-box avoidance in the rat. Psychopharmacology (Berl) 1984; 84: 476-9.

[67] Stiglick A, Kalant H. Residual effects of chronic cannabis treatment on behavior in mature rats. Psychopharmacology (Berl) 1985; 85: 436-9.

[68] Schneider M, Koch M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neuropsychopharmacology 2003; 28: 1760-9.

[69] O'Shea M, McGregor IS, Mallet PE. Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar long-lasting deficits in object recognition and reduced social interaction in rats. J Psychopharmacol 2006; 19: 19.

[70] O'Shea M, Singh ME, McGregor IS, Mallet PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. J Psychopharmacol 2004; 18: 502-8.

[71] Cha YM, White AM, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of delta9-THC on learning in adolescent and adult rats. Pharmacol Biochem Behav 2006; 83: 448-55.

[72] Quinn HR, Matsumoto I, Callaghan PD, *et al*. Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. Neuropsychopharmacology 2007.

[73] Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend 2003; 69: 303-10.

[74] Wechsler D. Manual for the Wechsler Adult Intelligence Scale-Revised. Cleveland, OH: Psychological Corporation 1981.

[75] Luria AR. Higher cortical functions in man. New York: Basic Books 1966.

[76] Lynskey M, Hall W. The effects of adolescent cannabis use on educational attainment: a review. Addiction 2000; 95: 1621-30.

[77] Skosnik PD, Krishnan GP, Vohs JL, O'Donnell BF. The effect of cannabis use and gender on the visual steady state evoked potential. Clin Neurophysiol 2006; 117: 144-56.

[78] Ehrenreich H, Rinn T, Kunert HJ, *et al*. Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology (Berl) 1999; 142: 295-301.

[79] Kempel P, Lampe K, Parnefjord R, Hennig J, Kunert HJ. Auditory-evoked potentials and selective attention: different ways of information processing in cannabis users and controls. Neuropsychobiology 2003; 48: 95-101.

[80] Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. J Addict Dis 2000; 19: 1-22.

[81] Biscaia M, Marin S, Fernandez B, *et al*. Chronic treatment with CP 55,940 during the peri-adolescent period differentially affects the behavioural responses of male and female rats in adulthood. Psychopharmacology (Berl) 2003; 170: 301-8.

[82] Gruber AJ, Pope HG, Jr. Marijuana use among adolescents. Pediatr Clin North Am 2002; 49: 389-413.

[83] Henquet C, Krabbendam L, de Graaf R, ten Have M, van Os J. Cannabis use and expression of mania in the general population. J Affect Disord 2006; 95: 103-10.

[84] Henquet C, Krabbendam L, Spauwen J, *et al*. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 2005; 330: 11.

[85] Medina KL, Shear PK. Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use. Drug Alcohol Depend 2007; 87: 303-11.

[86] Agosti V, Nunes E, Levin F. Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. Am J Drug Alcohol Abuse 2002; 28: 643-52.

[87] Tapert SF, Schweinsburg AD, Barlett VC, *et al*. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. Alcohol Clin Exp Res 2004; 28: 1577-86.

[88] de Bruin EA, Stam CJ, Bijl S, Verbaten MN, Kenemans JL. Moderate-to-heavy alcohol intake is associated with differences in synchronization of brain activity during rest and mental rehearsal. Int J Psychophysiol 2006; 60: 304-14.

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